

INTERACTION ANALYSES OF LIVE, ATTENUATED TETRAVALENT DENGUE VACCINES - EVIDENCE OF INTERFERENCE AND COMPLEMENTATION

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Live, multivalent vaccines may exhibit interference in human subjects. To identify possible interactions and optimize doses for tetravalent dengue vaccines, four dengue (DEN) vaccine viruses were administered to volunteers as: 1) full dose monovalent vaccines (n=31) and 2) 16 tetravalent vaccine formulations derived from a factorial design with all combinations of full and low dose dengue vaccines (n=61). For the factorial analyses, increasing the dose of DEN-1, DEN-3, or DEN-4 resulted in significantly increased geometric mean titers (GMTs) to that serotype. For DEN-2, the GMT was higher with a low dose of DEN-2. DEN-1 and DEN-3 exhibited mutual interference at full doses, while a full dose of DEN-3 boosted GMTs to DEN-4. The greatest reactogenicity was observed when DEN-1 was at full dose and all others were low; the addition of other serotypes at full doses decreased the reactogenicity of the formulation. The lowest reactogenicity was observed when all serotypes were at full dose. Data comparing monovalent vaccines to full dose tetravalent formulations are pending. These findings were tested against new dose formulations with vaccine viruses of earlier passage history. The model correctly predicted that increasing the dose of DEN-1 was associated with increased GMTs to DEN-1, 2, and 3 (direct relationship). An inverse relationship was observed with an increased dose of DEN-1 and GMTs to DEN-4. This conflicted with model predictions but may be attributable to the difference in passage history. The model correctly predicted that reactogenicity would decrease with a higher dose of DEN-1. These data suggest that viral interaction occurs in tetravalent dengue vaccine formulations, with respect to both antibody titers and reactogenicity. Both interference and enhancement were observed in antibody responses. Interestingly, increasing the dose of non-DEN-1 serotypes decreased adverse effects of the vaccine. Factorial designs may be useful in designing optimal vaccine formulations by predicting the effects of changes in dose.

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METHODOLOGY OF THE PROSPECTIVE STUDY OF DENGUE VIRUS TRANSMISSION AND DISEASE IN PRIMARY SCHOOL AND VILLAGE CHILDREN IN KAMPHAENG PHET, THAILAND

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An improved understanding of the correlations between the host, viral, and environmental factors and dengue disease severity will contribute to dengue virus (DV) vaccine development. The goal of the study is to identify factors that have the strongest influence in determining the early events in acute DV infections, and the eventual clinical manifestations of disease. An